DYSKERATOSIS CONGENITA; A CASE REPORT AND REVIEW OF LITERATURE

*** Latha Mary Cherian, ** Deepthi. K, *** Rejani. E.R**

**Asst Professor, **Sr. Resident , Dept of Oral Pathology, Govt Dental College, Kottayam.India*

****Lecturer, Dept of Oral Medicine, Govt Dental College, Kottayam.*

Abstract:

Dyskeratosis congenita, a rare inherited condition, is estimated to occur in 1 in 1 million people. The disease is characterised by a classic triad: nail dystrophy, reticulate skin pigmentation, and oral leukoplakia. These patients may also exhibit variable extend of pulmonary, gastrointestinal, genitourinary, cerebral, and dental involvement. Early mortality is often associated with bone marrow failure, infections, fatal pulmonary complications, or malignancy. More than 200 individuals have been reported in the literature with dyskeratosis congenita. Since most cases are inherited as X linked recessive disorder DKC in female is rare. Here we present a case of dyskeratosis congenita in a 16 year old female patient, who presented all features of classic triad and few additional skeletal features as well.

Introduction:

Dyskeratosis congenita (DKC), otherwise known as Zinsser-Engman-Cole syndrome[1], is a multisystem genodermatosis characterized by network-like dark patches, abnormal nail growth, lesions in the mouth, progressive bone marrow failure, pulmonary disease and an increased risk of malignancy. DKC continues to stimulate clinical and research interest because, although estimated to occur in 1 in 1 million people,[2] it is devastating for the patient and his/her family. DKC is genetically heterogeneous, with X-linked recessive, autosomal dominant and autosomal recessive subtypes but majority of the cases show X-linked recessive inheritance. Because of this type of inheritance pattern, the ratio of men to women affected by the disorder is approximately 10:1. DKC is caused by a mutated gene, DKC1, located on the X chromosome. The mucocutaneous features of DKC typically develop between ages 5 and 15 years.

Case Report:

A sixteen year old female reported to the dental college with a chief complaint of decayed teeth and pigmented areas in various regions of her mouth. History revealed that she exhibited hyper pigmentation of the arms and legs (fig 1 & fig 2) as well. She had defective fingernails and toenails (fig 3 & fig 3) from birth. Since the age of ten, patient has been taking medicine for inter vertebral disc prolapse and recently she was diagnosed with gastric ulcer. The parents had no similar

abnormalities. Her general health had been excellent and she had normal intelligence.

Intra oral examination revealed hyper pigmentation of the tongue, keratotic white patches on the buccal mucosa, and multiple caries exposed teeth (fig 5). On extra oral examination, reticulate hyper pigmentation and thickening of the skin of forehead, hands and legs, dystrophy of nails of all digits and premature aging were noticed.

The routine laboratory tests were negative or within normal limits. Incision biopsy taken from buccal mucosa and skin were submitted for conventional histopathologic examination. Histopathology of the skin was consistent with acrokeratosis where the section showed hyperkeratosis (fig 7), mild acanthosis and thickened collagen bundles (fig 8). On the contrary, oral mucosa showed both hyper parakeratotic and atrophic areas (fig 5). The connective tissue stroma of oral mucosa was densely collagenous and numerous melanophages were noticed in the juxta epithelial area (fig 6).

Discussion:

Dyskeratosis congenita (DKC), an inherited syndrome, first described by Zinsser in 1910, is characterized by the triad of reticulated skin hyperpigmentation, nail dystrophy (both occurring in 100% of cases), and white plaques (80% of cases); typically occurring in the oral cavity.[1] Other features occur with lower frequencies and involve virtually every organ system.[2] The main causes of death are bone marrow failure/immunodeficiency (~60-70%), pulmonary complications (~10-15%), and malignancy (~5-10%).[3]

DKC is related to telomerase dysfunction; all genes associated with this syndrome (DKC1, TERC, TERT, TINF2 and NOP10) encode proteins in the telomerase complex responsible for maintaining telomeres at the ends of chromosomes. Patients with DKC have reduced telomerase activity and abnormally short tracts of telomeric DNA compared with normal controls. Telomeres are repeat structures found at the ends of chromosomes that function to stabilize chromosomes, they have critical role in preventing cellular senescence and cancer progression. The defective telomere maintenance in DKC results in chromosomal shortening and gene loss during cell replication which ultimately leads to cell apoptosis, particularly in highly proliferative tissues such as the hematologic and dermatologic systems.[4]

Two subsets of DKC have been reported;

1. Hoyeraal-Hreidarsson (HH) Syndrome; where the clinical findings are consistent with DKC, plus intrauterine growth retardation, developmental delay, microcephaly, cerebellar hypoplasia, immunodeficiency, and bone marrow failure.

2. Revesz Syndrome: Findings similar to HH, plus a specific finding in the eye, called "exudative retinopathy."

The typical symptoms of dyskeratosis congenita involve the skin, nails, and mucous membranes, as well as bone marrow failure. The cutaneous presentation is abnormal skin pigmentation with tan-to-gray hyperpigmented or

hypopigmented macules and patches in a mottled or reticulated pattern, which may clinically and histologically resemble graft versus host disease. The typical distribution involves the sun-exposed areas, including the upper trunk, neck, and face as seen in our patient.[7] Other cutaneous findings may include alopecia of the scalp, eyebrows, and eyelashes; premature graying of the hair; hyperhidrosis; hyperkeratosis of the palms and soles; and adermatoglyphia (loss of dermal ridges on fingers and toes).

Nail dystrophy, the first component of the syndrome to appear, is seen in approximately 90% of patients, with fingernail involvement often preceding toenail involvement. Progressive nail dystrophy begins with ridging and longitudinal splitting. Progressive atrophy, thinning, and distortion eventuate in small, rudimentary, or absent nails.[8] In mild cases ridging and longitudinal fissuring occur. In our patient all the toe and finger nails were dystrophic from birth itself.

Though mucosal leukoplakia commonly involves the buccal mucosa, tongue, and oropharynx, it may also be seen in areas like esophagus, urethral meatus, glans penis, lacrimal duct, conjunctiva, vagina, anus etc. Constriction and stenosis can occur at the later mentioned sites, with subsequent development of dysphagia, dysuria, phimosis, and epiphora. The leukoplakia may become verrucous, and ulceration may occur.[9] Leukoplakia of the buccal mucosa and hyper pigmentation of the tongue were found in our patient.

Bone marrow failure is a major cause of death, with approximately 70% of deaths related to bleeding and opportunistic infections as a result of bone marrow failure. Approximately 90% have peripheral cytopenia of one or more lineages. In some cases, this is the initial presentation, with a median age of onset of 10 years.[6] There was no hematological abnormality in our patient.

Individuals with dyskeratosis congenita may also be presented with gastrointestinal system findings like hepatosplenomegaly and cirrhosis and pulmonary complications, including pulmonary fibrosis and abnormalities of pulmonary vasculature.

Other symptoms such as an increased prevalence and severity of periodontal disease, increased incidence of dental caries as in this patient, mandibular hypoplasia, osteoporosis, and scoliosis may be seen in these types of patients. Abnormalities of the CNS like low intelligence, small sella turcica and intracranial calcifications have also been reported.[3]

Patients have an increased prevalence of malignant mucosal neoplasms, particularly squamous cell carcinoma of the mouth, nasopharynx, esophagus, rectum, vagina, or cervix. These often occur within sites of leukoplakia and tend to develop in the third decade of life. The prevalence of squamous cell carcinoma of the skin is also increased. Other malignancies reported include Hodgkin lymphoma, adenocarcinoma of the gastrointestinal tract, and bronchial and laryngeal carcinoma.

DKC is usually diagnosed by taking in to account the findings on physical examination and with the help of telomerase length testing and mutation analysis; The type of DC with X-linked inheritance shows mutations in the gene called DKC1 whereas DC with autosomal dominant inheritance may be due to mutations in other genes called TERC, TERT and TINF2 and autosomal recessive type of DKC is

characterised by abnormal genes called NOP10 (also known as NOLA3).

The diagnosis of dyskeratosis congenita in our patient was supported by the presence of characteristic triad of pigmentary and atrophic changes of the skin, nail dystrophy and leukoplakia on the buccal mucosa. In addition, she had variety of minor manifestations like multiple carious teeth, gingivitis, hyperpigmentation of tongue, gastric ulcer, skeletal abnormalities and features of premature aging as have been described in earlier reports.

Currently there is no curative treatment for DKC. The variation in presentation makes it difficult to treat, with bone marrow failure/immunodeficiency being the main cause of premature mortality. Use of the anabolic steroid oxymetholone and haematopoietic growth factors such as erythropoietin (epoetin alpha), granulocyte macrophage colony-stimulating factor and granulocyte colony-stimulating factor (filgrastim) can produce improvement in the haematopoietic function.[11] Although the mechanism of action of oxymetholone is not well understood, it is thought to function by promoting the growth of haematopoietic progenitors indirectly through the effect of cytokine production and by supporting haemopoietic production in times of stress. The only long term cure for the haemopoietic abnormalities is allogeneic haematopoietic stem cell transplantation, but this is not without risk. There is still significant mortality associated with bone marrow transplants for DKC patients when compared with other bone marrow failure syndromes. One of the main reasons for this is the high level of pulmonary/vascular complications that present in these patients probably as a result of the underlying telomere defect.[12] Recently, the adoption of non-myeloablative fludarabine based protocols has allowed for successful engraftment in some patients with fewer complications and lower toxicity.

Conclusion:

The advances in our understanding of DKC have increased remarkably over the last 10 years but there are still huge advances to be made. The long-term survival however is unknown at present but the initial response is encouraging as a more effective treatment for DKC.

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Sorce of Support: Nil , **Conflict of Interest:** None declared

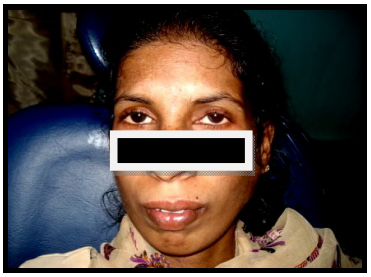

Fig 1 Hyperpigmentation on the forehead& nose

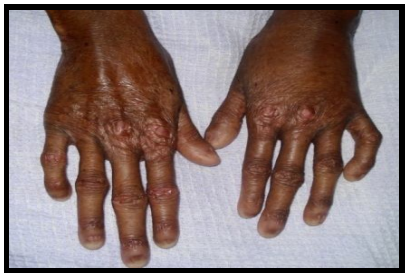

Fig 2 Nail dystrophy& Reticular hyperpigmentation

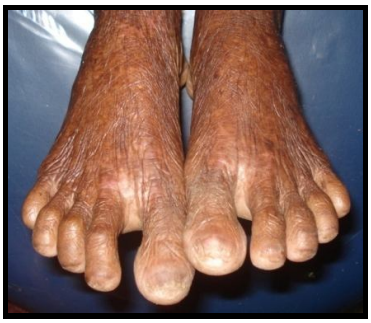

Fig 3 Nail dystrophy& Reticular pigmentation

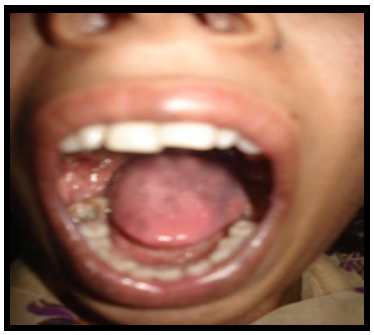

Fig 4 Hyperpigmentation of the tongue

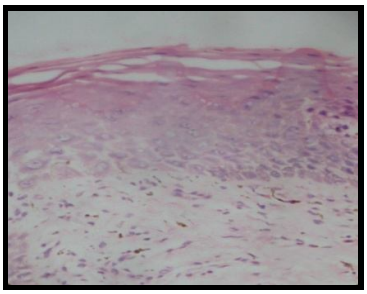

Fig 5 Buccal mucosa shows hyperkeratosis & atrophy

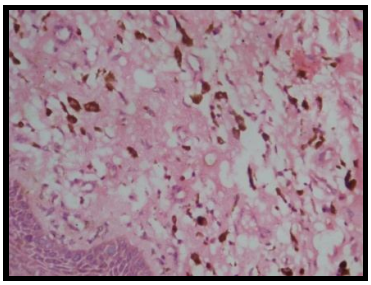

Fig 6 Lamina propria with numerous melanophages

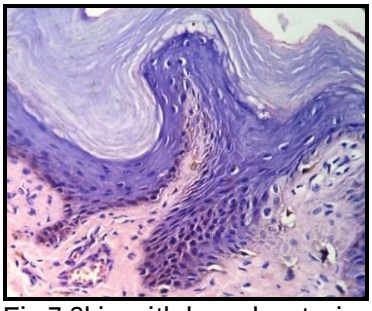

Fig 7 Skin with hyperkeratosis

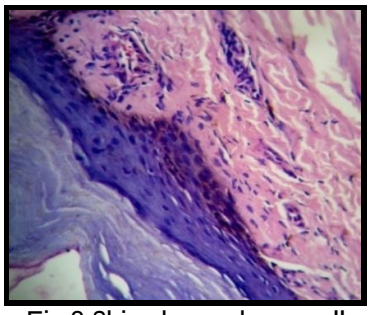

Fig 8 Skin shows dense collagen bundles in the stroma